REMARKS

Claims 1, 10, 12, 16 and 18 are amended herein. Support is found for example, in the original claims. Claim 6 is canceled. No new matter is presented.

I. Response to Rejection under 35 U.S.C. § 112, first paragraph

A. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification allegedly does not reasonably provide enablement for prevention and/or treatment of the claimed disorders for the full scope of compounds encompassed by claim 1.

Applicants traverse the rejection.

In the present Action, the Examiner states that Applicants have provided only a "single compound showing *in vitro* activity." See page 5 of the Office Action. The Examiner's assertion is incorrect. On pages 136-139 of the present specification, Applicants disclose several biological Experiments, including several formulations of compounds demonstrating antagonistic activity towards an LPA receptor as well as *in vivo* data showing the compound's effect on urethral pressure. As a means to further supplement this data, Applicants demonstrated Edg2 antagonistic activity for 12 additional compounds in the Declaration under 37 C.F.R. § 1.132 filed on August 11, 2009. Since it is shown in the specification of the present application that the compounds which show the pharmacological activity in vitro also decrease urethral pressure *in vivo*, the compounds described in the Declaration can be expected to have pharmacological function similarly *in vivo*.

The law pursuant to 35 U.S.C. § 112, First Paragraph, is that not every operable embodiment must be disclosed. Accordingly, Applicants' specification and § 1.132

Declaration provide a multitude of examples of compounds falling within the scope of the claim 16 such that one skilled in the art would be enabled to make and or use the claimed compound for treatment of urinary system disease selected from the group consisting of prostatic hypertrophy, neurogenic bladder dysfunction disease, dysuria, pollakiuria, night urination and urodynia.

Under U.S. practice, the test of enablement is whether one reasonably skilled in the art could make and/or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation. See *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The enablement requirement permits a substantial amount of screening and experimentation, as long as the experimentation is routine. Even extended periods of experimentation may not be undue if those of skill in the art are given sufficient direction or guidance as to how the experimentation should proceed. See *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

Moreover, Experimental methods described in the specification (measurement of EDG-2 antagonistic activity) are routine work for the person skilled in the art and are not undue experiments. Therefore, how to use the compounds for which pharmacological data are not disclosed can be confirmed using same measurement system. Specifically, at page 136 of Applicants' specification, a test to determine whether a compound has EDG-2 antagonistic activity is disclosed, demonstrating that it is routine in the art to test the compound prior to using it for treatment. Accordingly, the Examiner has not met his burden

of showing that the art, as it relates to the claimed compounds, is so unpredictable as to require undue experimentation.

In the Office Action, the Examiner relies on Kubinyi and Heasley et al to show that analogous compounds with minor variations in structure can have widely disparate levels of effectiveness.

The Examiner's reliance is misplaced.

While the compounds in the present application are antagonists of receptors, *Kubinyi* relates to binding mode of enzyme inhibitors. On the other hand, *Heasley* discloses compounds which have different structures and are non-selective LPA antagonists. Therefore, it cannot be said that compounds in the present application for which pharmacological effect are not shown have largely different activity according to substituent(s), based on the combination of the two publications.

More specifically, with regard to Kubinyi, the Examiner cites Kubinyi as teaching that the art is highly unpredictable. However, the portion of Kubinyi relied upon by the Examiner relates to multiple binding modes and aspects of enzyme inhibitor binding. The compounds in the present application are not enzyme inhibitors. As discussed in the responses of August 11 and September 11, 2009, it is inappropriate for the Examiner to reject claim 16 based on as Kubinyi is irrelevant to the claimed compounds.

To supplement prior assertions based on Kubinyi (i.e. that small changes in the structure of an LPA antagonist can have dramatic effects on the compound's antagonistic

activity), the Examiner cites to Heasley et al as teaching "analogue" compounds having LPA antagonistic activity. However, the Examiner's reliance on Heasley et al does not cure the deficiencies of Kubinyi or provide an independent basis to reject claim 16.

In particular, the Examiner cites to Heasley et al as teaching that minor substitutions on the phenyl rings of LPA antagonists can render the compounds inactive. However, the LPA antagonists of Heasley et al are dissimilar to the present compounds and thus cannot be relied upon as being "analogues" for the purposes of making a functional comparison.

In particular, Heasley et al disclose several *N*-acyl moiety-derivatives (4a-e) and ether/ester derivatives (10a-u) of the LPA_1/LPA_3 antagonist VPC12249. Based on the IC_{50} value of these derivatives, the Examiner broadly asserts that "small structural changes in LPA antagonists can have radical effects on the activity of a compound," (page 7 of the Office Action) and can even "render the compound inactive" (page 4 of the Office Action).

There are two deficiencies with the Examiner's above reliance on Heasley et al. First, the LPA antagonists of Heasley et al were designed as multifunctional LPA receptor antagonists and subsequently measure both LPA_1(Edg2) and LPA_3 (Edg7) IC_{50} data. In contrast, the present compounds antagonize the Edg2 receptor, thus any conclusions based on LPA_3 are simply irrelevant.

Second, and most significantly, the Heasley et al compounds do not read on the present claims. Specifically, the present compounds have ring moieties on substituents A, B, D, and E. In contrast, none of the compounds disclosed in Heasley et al have ring moieties on the A substituent. Accordingly, the Examiner's statement that the Heasley et al

compounds and the present compounds are "analogous" is misplaced. It follows that any conclusion relying on that premise is also misplaced. There is no evidence that the Heasley et al compounds and the present compounds would be expected to behave similarly in spite of this clear structural difference.

When addressing the IC_{50} data presented in Applicants' § 1.132 Declaration, the Examiner states that "the conclusion of unpredictability…is also supported by the variations in the IC_{50} data…because the values vary by more than an order of magnitude even with only minor structural variations.

The Examiner's conclusion is again misplaced and legally unsupported.

In one respect, it is true that IC_{50} data values in Applicants' § 1.132 Declaration vary according to each compound. However, it is expected that some compounds will exhibit superior results over other closely-related compounds. Furthermore, the fact that each compound exhibits a particular effectiveness is also expected; it is not necessary for Applicants to demonstrate that each compound exhibits the same effectiveness.

Accordingly, based on the weight of the evidence, it is clear that the compounds in the present application are effective for specific urinary system diseases recited in present claim 16 and that present invention enables the person skilled in the art to use the present invention, without undue experimentation.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, 1st paragraph are respectfully requested.

B. Claims 1, 2, 5-7, 9, 10, 12, 13, 15, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds identified as having inhibitory effect with experimental data, allegedly does not reasonably provide enablement for the asserted utility of the entirety of the claim scope essentially for the same reasons as set forth above with minor variations.

Applicants traverse the rejection for the reasons set forth above and additionally based on the following.

At page 8 of the Action, the Examiner identifies the compound on page 137 as Applicants' only showing of *in vitro* data (IC_{50}). As discussed above, the Examiner is incorrect. Applicants have provided *in vivo* and *in vitro* data for several compounds both in the specification and in the § 1.132 Declaration submitted on September 11, 2009.

Further, the Examiner contends that the critical element to this enablement rejection is "how broad the claims are compared to the level of unpredictability in the art," and cites to Kubinyi and Heasley et al as teaching that small variations in structure can lead to "radical effects on the binding of an inhibitor." See page 8 of the Office Action.

In this connection, the Examiner contends that the evidence in Kubinyi and Heasley et al supports the assertion that one skilled in the art could not "predict *a priori* whether a given pharmaceutical would affect an enzyme."

The Examiner's conclusion is again misplaced. First, the Examiner continues to refer to an "enzyme," presumably in response to the teachings of Kubinyi which discuss enzymes. However, the claimed compounds have antagonistic activity on LPA receptors and are different

from the enzymes of Kubinyi. Moreover, in contrast to the compounds disclosed in Heasley et al, every compound disclosed by Applicants in the specification and § 1.132 Declaration exerts a specific antagonistic activity.

Thus, the Examiner's statement that it is impossible to predict *a priori* whether each compound would have activity is unfounded. It is considered that the Examiner makes this statement in response to the teachings of Heasley et al, wherein several enzymes do not exhibit effective IC_{50} values, even when supplied at a high concentration. However, as discussed above, the compounds in Heasley et al (1) are designed as multifunctional LPA receptor antagonists and thus are different from the claimed compounds, and (2) do not read on the present claims.

Accordingly, by relying on the misplaced and defective comparisons of Kubinyi and Heasley et al, the Examiner has not met his burden of showing that the art is so unpredictable as to require undue experimentation.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 1st paragraph are respectfully requested.

C. Claims 1, 2, 5-7, 9-13, 15, 16, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for "solvates thereof."

The claims are amended herein by deleting recitations relating to "solvates", thereby obviating the rejection.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, 1st paragraph.

II. Response to Rejection under 35 U.S.C. § 102

Claims 1, 2, 6, 7, 9, 12, 13, 15, and 16 are rejected under 35 U.S.C. 102 (e) as allegedly being anticipated by US 2006/0148830 ('830).

The Examiner relies on Example 31 of '830 as teaching a compound that reads on the present claims.

Applicants traverse the rejection.

'830 is not legally effective prior art under 35 U.S.C. § 102 (e), because the corresponding PCT was not published in English.

Pursuant to MPEP 706.02(f)(1), a reference based upon the national stage of an International Application not published in English under PCT article 21(2) cannot claim the international date of filing as its § 102 (e) date.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(e).

III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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